Japan H6-279488

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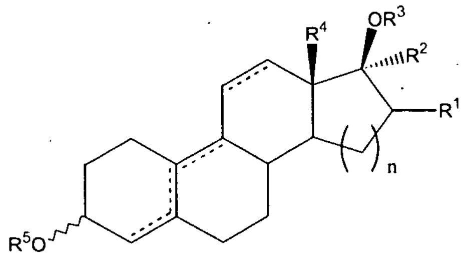
(54) Title of the Invention

Novel steroid derivatives and drugs for the treatment of osteoporosis

(57) Abstract (amended)
Constitution:

Steroid derivatives which can be represented by formula (1) indicated below.



(In this formula R^1 and R^2 represent (substituted) lower hydrocarbyl groups, OR^3 represents a hydroxyl group or a protected hydroxyl group, R^4 represents a (substituted) lower hydrocarbyl group, OR^5 represents an α- or β- hydroxyl group or protected hydroxyl group and n represents 1 or 2, and the bonds indicated with a broken line part represent single bonds or double bonds. However, either the bond in the 4-5 position or the bond in the 5-10 position represents a double bond.)

Effect:

The abovementioned steroid derivatives exhibit an excellent bone mass increasing action with very little in the way of side effects and so they are useful as safe drugs for the treatment of osteoporosis.

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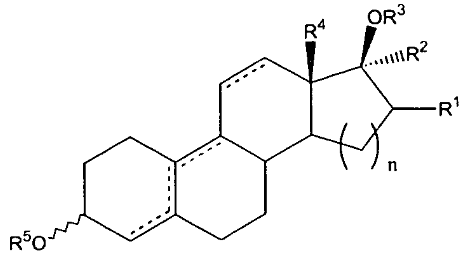
Scope of the Patent Claim

[Claim 1]

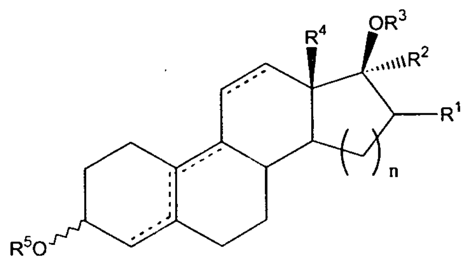


(1)

A steroid derivative which can be represented by the general formula (1) indicated below.

(In this formula R^1 and R^2 each represent an optionally substituted lower hydrocarbyl group, OR^3 represents a hydroxyl group or a protected hydroxyl group, R^4 represents an optionally substituted lower hydrocarbyl group, OR^5 represents an α- or β- hydroxyl group or protected hydroxyl group and n represents 1 or 2, and the bonds indicated with a broken line part represent single bonds or double bonds. However, either the bond in the 4-5 position or the bond in the 5-10 position represents a double bond.)

[Claim 2]



(1)

A drug for the treatment of osteoporosis which has a steroid derivative which can be represented by the general formula (1) indicated below as an effective component.

(In this formula R^1 and R^2 each represent an optionally substituted lower hydrocarbyl group, OR^3 represents a hydroxyl group or a protected hydroxyl group, R^4 represents an optionally substituted lower hydrocarbyl group, OR^5 represents an α- or β- hydroxyl group or protected hydroxyl group and n represents 1 or 2, and the bonds indicated with a broken line part represent single bonds or double bonds. However, either the bond in the 4-5 position or the bond in the 5-10 position represents a double bond.)

Detailed Description of the Invention

[0001]

Industrial Field of Application

The invention concerns novel steroid derivatives which have a bone mass increasing action and drugs for the treatment of osteoporosis which have these derivatives as effective components.

[0002]

Prior Art

Osteoporosis is a disease or abnormal state where the balance of bone absorption and bone formation is disturbed by metabolic impairment, endocrinopathy, ageing or the like giving rise to a state, or giving rise to the risk of a state, where the bone mass is reduced. The principal signs are dorsolumbar pains, deformation of the spine and fracture of the femur. In the past estrogen preparations, calcitonin preparations, vitamin D preparations and calcium preparations have been used as therapeutic agents.

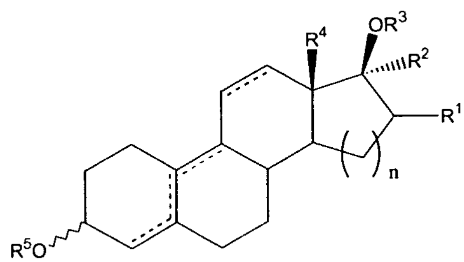
[0003]

Problems to be Resolved by the Invention

However, the estrogen preparations which have been used in the past have had an associated risk or causing the onset of cancer, calcitonin preparations cannot be administered orally, vitamin D preparations have the potential to cause hypercalcemia and calcium preparations must be administered in large amounts and so suitable cases for these drugs are limited and there are cases where the effect is inadequate, and there is a demand for a therapeutic agent which is more effective and with little in the way of side effects.
[0004][0005][0006]

Means of Resolving These Problems

The inventors have realized the present invention as a result of a thorough investigation carried out with a view to resolving the aforementioned problems. That is to say, in outline the invention concerns (1) steroid derivatives which can be represented by general formula (1) indicated below, and (2) drugs for the treatment of osteoporosis in which the aforementioned steroid derivatives which can be represented by general formula (1) form the effective components.



(1)

(In this formula R^1 and R^2 each represent an optionally substituted lower hydrocarbyl group, OR^3 represents a hydroxyl group or a protected hydroxyl group, R^4 represents an optionally substituted lower hydrocarbyl group, OR^5 represents an α- or β- hydroxyl group or protected hydroxyl group and n represents 1 or 2, and the bonds indicated with a broken line part represent single bonds or double bonds. However, either the bond in the 4-5 position or the bond in the 5-10 position represents a double bond.)
[0007] [0008]

[0009]

The "bonds indicated with a broken line part" are the bonds which are shown in the formula in the way indicated below.
[0010]

The optionally substituted hydrocarbyl groups represented by R^1 in general formula (1) include, for example, optionally substituted lower alkyl groups such as methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, isopropyl group, isobutyl group, sec-butyl group, cyclopentyl group, cyclohexyl group, methoxymethyl group, chloromethyl group, bromomethyl group, trifluoromethyl group and cyanomethyl group; optionally substituted lower alkenyl groups such as vinyl group, allyl group, propenyl group, 2-butenyl group, 3-butenyl group, pentenyl group, hexenyl group, isopropenyl group, 2-methylpropenyl group, cyclopentenyl group, 3-cyclohexenyl group and 2-bromovinyl group; optionally substituted lower alkynyl groups such as ethynyl group, propynyl group, 2-butynyl group, 3-butynyl group, pentynyl group, hexynyl group, chloroethynyl group, trifluoromethylethynyl group and propargyl group; optionally substituted aryl groups such as phenyl group, naphthyl group and 4-methoxyphenyl group;

optionally substituted aralkyl groups such as benzyl group and optionally substituted heterocyclic groups such as 2-thienyl group. In this invention no particular limitation is placed upon this group provided that it is a lower hydrocarbyl group, but the optionally substituted alkyl groups which have not more than 4 carbon atoms, the optionally substituted alkenyl groups which have not more than 4 carbons atoms and the optionally substituted alkynyl groups which have not more than 4 carbons atoms are preferred.

[0011]

The optionally substituted hydrocarbyl groups represented by R^2 in general formula (1) include, for example, optionally substituted lower alkyl groups such as methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, isopropyl group, isobutyl group, sec-butyl group, cyclopentyl group, cyclohexyl group, methoxymethyl group, chloromethyl group, bromomethyl group, trifluoromethyl group and cyanomethyl group; optionally substituted lower alkenyl groups such as vinyl group, allyl group, propenyl group, 2-butenyl group, 3-butenyl group, pentenyl group, hexenyl group, isopropenyl group, 2-methylpropenyl group, cyclopentenyl group, 3-cyclohexenyl group, 1,2-propadienyl group and 2-bromovinyl group; optionally substituted lower alkynyl groups such as ethynyl group, propynyl group, 2-butynyl group, 3-butynyl group, pentynyl group, hexynyl group, chloroethynyl group, 3-hydroxypropynyl, trifluoromethylethynyl group and propargyl group; optionally substituted aryl groups such as phenyl group, naphthyl group, 4-methoxyphenyl group, 4-dimethylaminophenyl group and 4-(2-dimethylaminoethyoxy)phenyl group; optionally substituted aralkyl groups such as benzyl group and optionally substituted heterocyclic groups such as furyl group and 2-thienyl group. In this invention no particular limitation is placed upon this group provided that it is a lower hydrocarbyl group, but the optionally substituted alkyl groups which have not more than 4 carbon atoms, the optionally substituted alkenyl groups which have not more than 4 carbons atoms and the optionally substituted alkynyl groups which have not more than 4 carbons atoms are preferred.

[0012]

R^3 and R^5 each represent a hydrogen atom or the protective group of a hydroxyl group. No particular limitation is imposed upon the protective group of a hydroxyl group which is represented by R^3 or R^5 provided that it has a satisfactory effect when the protective group has been introduced, and it may be, for example, a lower alkyl group such as methyl group, ethyl group and tert-butyl group; lower alkenyl groups such as allyl group; an optionally substituted aralkyl group such as a benzyl group; an optionally substituted heterocyclic group such as a tetrahydropyranyl group; an optionally substituted acyl group such as a formyl group, acetyl group, propionyl group, butyryl group, isobutyryl group, pivaloyl group, decanoyl group, stearoyl group, benzoyl group, phenoxyacetyl group, trichloroacetyl group and succinoyl group; or an alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group and benzyloxycarbonyl group. The optionally substituted acyl groups and optionally substituted alkoxycarbonyl groups are preferred.

[0013]

The optionally substituted lower hydrocarbyl groups represented by R^4 in general formula (1) include, for example, optionally substituted lower alkyl groups such as methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, isopropyl group, isobutyl group, sec-butyl group, cyclopentyl group, cyclohexyl group, methoxymethyl group, chloromethyl group, bromomethyl group, trifluoromethyl group and cyanomethyl group; optionally substituted lower alkenyl groups such as allyl group, 2-butenyl group, 3-

butenyl group and 3-cyclohexenyl group; lower alkynyl groups such as propargyl group, 2-butynyl group and 3-butynyl group and optionally substituted aralkyl groups such as benzyl group. No particular limitation is placed upon this group, but the optionally substituted alkyl groups which have not more than 3 carbon atoms are preferred.

[0014]

Compounds which can be represented by general formula (1) can be produced easily with the method indicated in reaction process I described below for example.

[0015]

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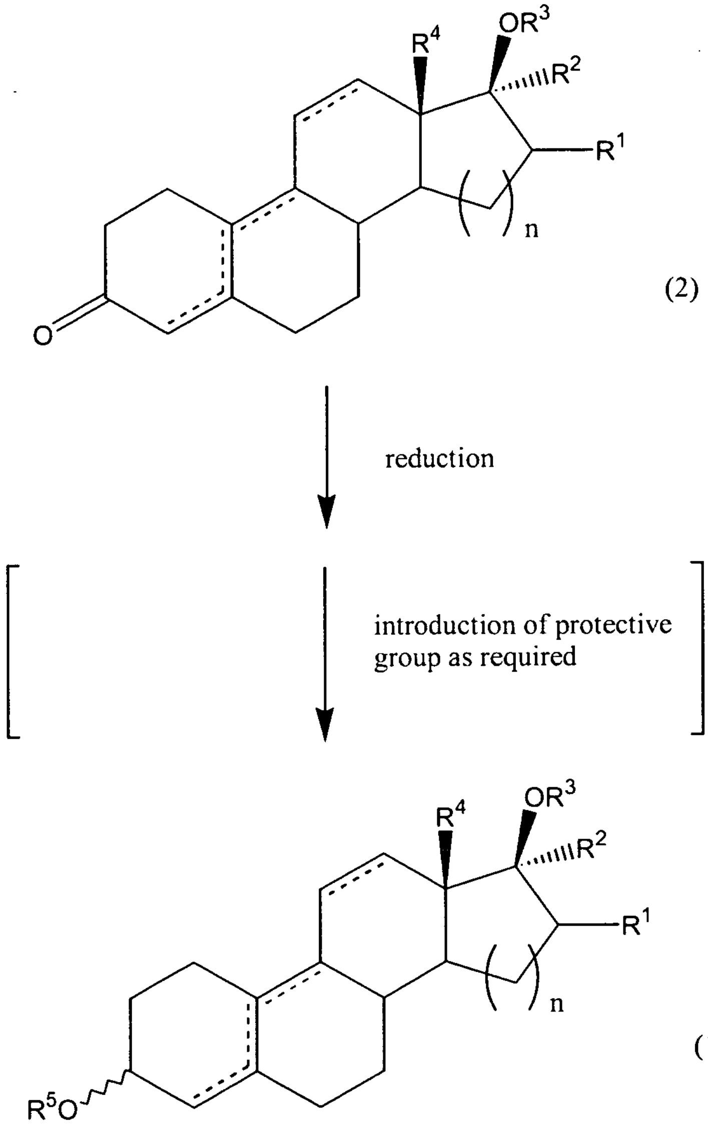
Reaction Process I



[0016]

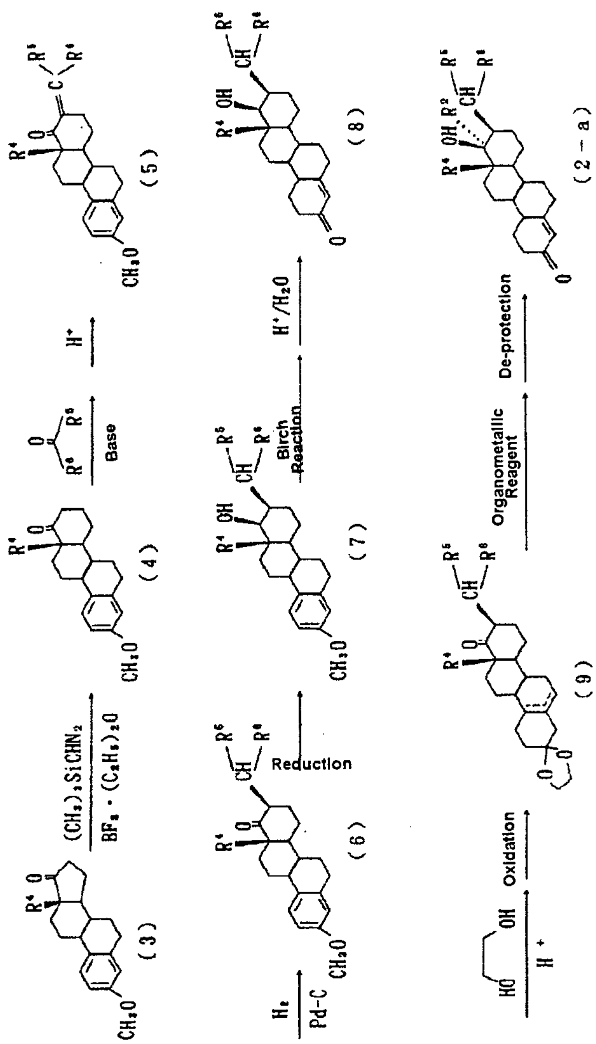
(In this formula R^1, R^2, R^3, R^4 R^5, n and the broken line have the same significance as before.)

[0017]

That is to say, the compounds can be produced by reducing a steroid derivative which can be represented by general formula (2) as the raw material compound using a reducing agent and introducing a protective group onto the 3-position hydroxyl group and/or 17-position hydroxyl group as required. The steroid derivative which can be represented by general formula (1) obtained can be subjected to de-protection or protection with protective groups in the usual ways. The steroid derivatives which can be represented by general formula (2) which are used for the starting material compounds are known compounds when n is 1 (Japanese Examined Patent Publication 49-16856) and they can be produced, for example, with the method shown in reaction process II indicated below in those cases where n is 2.

[0018]

Reaction Process II



[0019]
(In this reaction process, R^2 and R^4 are as defined earlier and R^5 and R^6 each individually represents a hydrogen atom or an optionally substituted lower alkyl group.)
[0020]
That is to say, the 3-methoxy-1,3,5(10)-oestratriene-17-one (compound (3)) represented by formula (3) is subjected to a ring-expansion reaction by reacting with trimethylsilyldiazomethane in the presence of a boron trifluoride ether complex to obtain the 3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one derivative (compound (4)) represented by formula (4). The said compound (4) is then reacted with a carbonyl compound selected from among the ketones and aldehydes in the presence of a basic catalyst and then, by means of an acid treatment, the 17-alkylidene-3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one derivative (compound (5)) represented by formula (5) is obtained. The alkylidene group in the 17-position of the said compound (5) is hydrogenated using a metal catalyst such as palladium/carbon to obtain the 17β-alkyl-3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one derivative (compound (6)) represented by formula (6). The carbonyl group in the 17a-position of compound (6) is then reduced with

a metal hydride complex compound. The 17β-ethyl-17aβ-hydroxy-3-D-homo-1,3,5(10)oestratriene derivative (compound (7)) represented by formula (7) so obtained is subjected to a Birch reduction followed by hydrolysis under acid conditions to form the 17β-alkyl-17aβ-hydroxy-D-homo-oestra-4-ene-3-one (compound (8)) represented by formula (8). The oxo group in the 3-position of the said compound (8) is then acetalated by reaction with ethylene glycol under acid conditions, for example, and the 17a-position is oxidized with dichromate or the like and a mixture of the 17β-alkyl-3-ethylenedioxy-D-homo-oestra-5-ene-17a-one derivative and the 17β-alkyl-3-ethylenedioxy-D-homo-oestra-5(10)-ene-17a-one derivative (compound (9)) represented by formula (9) is obtained. The said compound (9) is reacted with an organometallic reagent such as an organolithium reagent or Grignard reagent in the presence of cerium chloride and the 3-position protective group is eliminated and in those cases where the 17aα-hydroxyl group has a protective group this protective group is eliminated and in this way the 17β-alkyl-17aα-substituted-17aβ-hydroxy-D-homo-oestra-4-ene-3-one derivative represented by formula (2-a) can be obtained.

[0021]

No particular limitation is imposed upon the reducing agent which is used in the reduction reaction in Reaction Process I and, for example, di-isobutylaluminium hydride, sodium borohydride, lithium tri-s-butylborohydride, potassium tri-s-butylborohydride, lithium aluminum hydride, lithium tri-t-butoxyaluminium hydride, sodium bis(2-methoxyethoxy)aluminum hydride, 9-borabicyclo[3.3.1]nonane and the like can be used. The reduction reaction is carried out in the presence of an inert solvent, such as hexane, benzene, diethyl ether or tetrahydrofuran for example. The reaction temperature differs according to the type of reducing agent which is being used but the reaction is generally carried out at a temperature from -100°C to 150°C over a period of time ranging from about 1 minute to 1 day.

[0022]

The introduction of the hydroxyl group protective group in Reaction Process I should be carried out using any known method, and it can be achieved, for example, using the method described in Protective Groups in Organic Synthesis, Volume 2, (John Wiley & Sons, Inc., 1991). In those cases where the 3-position hydroxyl group or protected hydroxyl group is a mixture of α- and β- configurations these configurations can also be separated as required. The separation can be carried out with the usual means of organic chemistry, for example with the independent or conjoint use of methods such as column chromatography, high speed liquid chromatography, recrystallization and the like. Furthermore, the 3-position substituent groups with α- and β-configurations can be interchanged by means of a Mitsunobu reaction for example.

[0023]

The usual methods for the separation and refinement of organic compounds can be used for the separation from the reaction liquid and refinement of the steroid derivatives represented by general formula (1) obtained in this way. For example, the reaction mixture is treated with water, dilute hydrochloric acid, aqueous ammonium chloride solution or the like, extracted with an organic solvent such as diethyl ether or ethyl acetate, the liquid extract is washed sequentially with sodium bicarbonate solution, salt water and the like and then dried using anhydrous magnesium sulfate or anhydrous sodium sulfate for example and then concentrated to obtain the crude product, and the said crude product is then refined by means such as recrystallization, chromatography and the like and a steroid derivative represented by general formula (1) is obtained.

[0024]

The steroid derivatives of this invention which can be represented by general formula (1) exhibit an excellent bone mass increasing action and, moreover, they exhibit little toxicity and few side effects and so they are useful as safe drugs for the treatment of osteoporosis. Hence, they can be used effectively as safe drugs for the treatment of osteoporosis in mammals, including man.

[0025]

The drugs for the treatment of osteoporosis which have steroid derivatives which can be represented by general formula (I) as effective components can be administered orally or non-orally as medicinal drug composition of an appropriate form. The dose rate differs according to age, the signs and the mode of administration but when administered for the prevention or treatment of osteoporosis in an adult the dose rate is generally from 0.01 mg to 1,000 mg, and preferably from 0.1 mg to 100 mg administered with division into from 1 to 3 doses, per day for an adult, but of course the abovementioned range may be exceeded in accordance with any diagnosis made by a doctor.

[0026]

The drugs for the treatment of osteoporosis of this invention may contain an effective amount of the steroid derivative which is the effective component and pharmacologically permissible carrier or excipient. Compositions of this type can be provided in a form which is suitable for oral or for non-oral administration.

[0027]

That is to say, as compositions for oral administration they can have a solid or liquid form, and in practical terms they may take the form of tablets, pills, granules, water dispersible powders, capsules, syrups, emulsions, suspensions and the like. Such compositions can be produced using known methods, and the known carriers and excipients which are generally used in the field of such preparations may be included. For example, carriers and excipients for use in tablets include lactose, starch, sucrose and magnesium stearate.

[0028]

Taking injectables as an example of the compositions for non-oral administration, these can be prepared in accordance with the usual methods by dissolution, suspension or emulsification in an aqueous or oil-based liquid which is normally used for injectable drugs. The aqueous liquids for injection purposes include isotonic liquids such as physiological saline solution and those which contain other auxiliary materials such as glucose for example, and these may be used conjointly with a suitable dissolution promotor for example.

[0029]

Such drugs for the treatment of osteoporosis of this invention may also include other active components provided that these do not have an undesirable interaction with the formulation of the steroid derivative of this invention.

[0030]

Illustrative Examples

The invention is described in more detail below by means of illustrative examples, examples of testing and examples of preparation formulations, but the invention is not limited by these illustrative examples etc.

[0031]

Example 1

The Synthesis of 16β,17α-Diethyloestra-4-ene-3β,17β-diol

A tetrahydrofuran solution (30 ml) of 2.0 g of 16β-17α-diethyl-17β-hydroxyoestra-4-ene-3-one was added dropwise, with ice cooling, to 30 ml of a tetrahydrofuran suspension of 5.1 g of lithium tri-t-butoxyaluminium hydride and then the mixture was stirred for 4 hours with ice cooling. Water was added to the reaction mixture so obtained and the mixture was extracted with ethyl acetate and then the organic layer was washed with saturated salt water and dried with anhydrous sodium sulfate. The residue obtained on distilling off the solvent was subjected to silica gel column chromatography (hexane : ethyl acetate (2 : 1) as eluting solvent) and then recrystallized from methylene chloride/hexane and 1.50 g of the title compound which had the physical property values indicated below were obtained in the form of colorless crystals (yield 75%).

Melting Point: 131 - 133°C

^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.84 (3H, s), 0.92 (6H, t, J = 8 Hz), 4.1-4.2 (1H, m), 5.37 (1H, s)

[0032]

Example 2

The Synthesis of 17α-ethyl-16β-isopropyloestra-4-ene-3β,17β-diol

A tetrahydrofuran solution (30 ml) of 2.24 g of 17α-ethyl-16β-isopropyl-17β-hydroxyoestra-4-ene-3-one was added dropwise, with ice cooling, to 30 ml of a tetrahydrofuran suspension of 8.25 g of lithium tri-t-butoxyaluminium hydride and then the mixture was stirred for 4.5 hours with ice cooling. Water was added to the reaction mixture so obtained and the mixture was extracted with ethyl acetate and then the organic layer was washed with saturated salt water and dried with anhydrous sodium sulfate. The residue obtained on distilling off the solvent was subjected to silica gel column chromatography (hexane : ethyl acetate (2 : 1) as eluting solvent) and then recrystallized from methylene chloride/diethyl ether/hexane and 1.22 g of the title compound which had the physical property values indicated below were obtained in the form of colorless crystals (yield 54%).

Melting Point: 82.5 - 83°C

^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.86 (3H, s), 0.91 (3H, d, J = 7 Hz), 0.94 (3H, t, J = 7 Hz), 1.11 (3H, d, J = 7 Hz), 4.15 (1H, m), 5.38 (1H, s)

[0033]

Example 3

The Synthesis of 16β,17α-Diethyloestra-4-ene-3α,17β-diol

A tetrahydrofuran solution (8 ml) of 1.28 g of diethyl azodicarboxylate was added dropwise to 40 ml of a tetrahydrofuran solution of 1.93 g of the 16β-17α-diethyloestra-4-ene-3β,17β-diol obtained in Example 1 and 0.90 of benzoic acid. After stirring for 1 hour at room temperature the solvent was distilled off and the residue obtained was subjected to silica gel column chromatography (hexane : ethyl acetate (85 : 15) as eluting solvent). Ethanol (40 ml) and 10 ml of 1N sodium hydroxide aqueous solution were added to the 3α-benzoic acid ester so obtained and the mixture was stirred overnight at room temperature. Ethyl acetate and water were added to the reaction liquid so obtained and the mixture was partitioned and the organic layer obtained was washed with salt water and dried with anhydrous sodium sulfate. The solvent was distilled off and the residue obtained was subjected to silica gel column chromatography (hexane/ethyl acetate (2 : 1) as eluting solvent) and then recrystallized from methylene chloride/hexane and 0.74 g of

the title compound which had the physical property values indicated below was obtained in the form of colorless flocculant crystals (yield 63%).
Melting Point: 149 - 151°C
^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.86 (3H, s), 0.93 (6H, t, J = 8 Hz), 4.1-4.2 (1H, m), 5.56 (1H, d, J = 5 Hz)
[0034]
Reference Example 1
The Synthesis of 3-Methoxy-D-homo-1,3,5(10)-oestratriene-17a-one

Trimethylsilyldiazomethane (10% hexane solution) (100 ml) was added dropwise, with ice cooling, to a solution of 12.0 g of 3-methoxy-1,3,5(10)-oestratriene-17-one, 7.7 ml of boron trifluoride ether complex and 133 ml of methylene chloride. After stirring for 2 hours, with ice cooling, ice water was added and the mixture was stirred for a while. The mixture was then extracted with methylene chloride and washed sequentially with sodium bicarbonate solution and dilute salt water and then dried with anhydrous sodium sulfate. The solvent was distilled off and then the residue was dissolved in a mixture of methanol and tetrahydrofuran, 12 ml of concentrated hydrochloric acid were added and the mixture was stirred for 1 hour at room temperature. The solvent was distilled off under reduced pressure and then water was added and the mixture was extracted with methylene chloride. The organic layer was washed sequentially with sodium bicarbonate solution and dilute salt water and then dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was subjected to column chromatography (silica gel, 500 g) using ethyly acetate/hexane (1 : 7) as the developing solvent and 5.91 g of the title compound which had the physical property values indicated below was obtained as a white solid (yield 47%).
^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 1.12 (3H, s), 2.85 (2H, m), 3.78 (3H, s), 6.63 (1H, d, J = 3 Hz), 6.71 (1H, dd, J = 3 Hz and 9 Hz), 7.21 (1H, d, J = 9 Hz)
[0035]
Reference Example 2
The Synthesis of 17-Ethylidene-3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one

n-Butyl lithium (1.6M/hexane solution) (14 ml) was added at -70°C under an argon atmosphere to a solution of 3.97 ml of diisopropylamine and 35 ml of anhydrous tetrahydrofuran and stirred for 1 hour. A solution obtained by dissolving 5.91 g of the 3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one obtained in Reference Example 1 in 50 ml of anhydrous tetrahydrofuran was then added dropwise to the abovementioned solution at -70°C. The mixture was stirred for 30 minutes and then 3.3 ml of acetaldehyde was added dropwise at the same temperature and the mixture was stirred for 1 hour. The reaction liquid so obtained was poured into water and extracted with ethyl acetate and the organic layer was washed sequentially with dilute hydrochloric acid, sodium bicarbonate solution and saturated salt water and then dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was subjected to column chromatography (silica gel, 350 g) using ethyl acetate/hexane (20 : 80) as the developing solvent. The white solid so obtained (4.9 g) was dissolved in 300 ml of benzene, 127 mg of p-toluenesulfonic acid mono-hydrate were added and water was removed azeotropically under reflux for 2 hours using Dean and Stark apparatus. Ethyl acetate was added to the reaction liquid so obtained and, after washing sequentially with sodium bicarbonate solution and salt water, the mixture was dried with anhydrous sodium sulfate. When the solvent was distilled off 4.56 g of the title compound which had the physical property values indicated below were obtained as a light yellow colored solid (yield 71%).

^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 1.02 (3H, s), 1.73 (3H, d, J = 8 Hz), 2.85 (2H, m), 3.79 (3H, s), 6.58 (1H, m), 6.63 (1H, d, J = 3 Hz), 6.71 (1H, dd, j = 3 Hz and 9 Hz), 7.23 (1H, d, J = 9 Hz)

[0036]

Reference Example 3

The Synthesis of 17β-Ethyl-3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one

The 17-ethylidene-3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one obtained in Reference Example 2 was dissolved in a mixture of 250 ml of tetrahydrofuran and 200 ml of ethanol, 917 mg of 10% palladium/carbon were added and the mixture was hydrogenated overnight under normal pressure at room temperature. The reaction mixture so obtained was filtered using Celite, the solvent was distilled off and then column chromatography (silica gel, 300 g) was carried out using ethyl acetate/hexane (1 : 10) as the developing solvent and 4.47 g of the title compound which had the physical property values indicated below were obtained as a white solid (yield 97%).

^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.91 (3H, t, J = 8 Hz), 1.02 (3H, s), 2.86 (2H, m), 3.79 (3H, s), 6.63 (1H, d, J = 3 Hz), 6.72 (1H, dd, J = 3 Hz and 9 Hz), 7.21 (1H, d, J = 9 Hz)

[0037]

Reference Example 4

The Synthesis of 17β-Ethyl-17aβ-hydroxy-3-methoxy-D-homo-1,3,5(10)-oestratriene

A liquid suspension of 11.54 g of lithium tri(t-butoxy)aluminum hydride and 160 ml of anhydrous tetrahydrofuran was ice cooled under an inert gas atmosphere and 80 ml of an anhydrous tetrahydrofuran solution of 4.94 g of the 17β-ethyl-3-methoxy-D-homo-1,3,5(10)-oestratriene-17a-one obtained in Reference Example 3 was added dropwise and the mixture was stirred for 3 hours with ice cooling. Water was added to the reaction liquid so obtained and the mixture was extracted with ethyl acetate, after which the organic layer was washed sequentially with an aqueous solution of Rochelle salts and salt water and dried with anhydrous sodium sulfate. The solvent was distilled off and the residue was subjected to column chromatography (silica gel, 750 g) using ethyl acetate/hexane (1 : 6) as the developing solvent and 4.23 g of the title compound which had the physical property values indicated below were obtained as a white solid (yield 85%).

^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.82 (3H, s), 0.91 (3H, t, J = 8 Hz), 2.84 (2H, m), 3.39 (1H, d, J = 5 Hz), 3.78 (3H, s), 6.61 (1H, d, J = 3 Hz), 6.71 (1H, dd, J = 3 Hz and 9 Hz), 7.21 (1H, d, J = 9 Hz)

[0038]

Reference Example 5

The Synthesis of 17β-Ethyl-17aβ-hydroxy-D-homo-oestra-4-ene-3-one

A solution where the 4.23 g of 17β-ethyl-17aβ-hydroxy-3-methoxy-D-homo-1,3,5(10)-oestratriene obtained in Reference Example 4 and 10 ml of t-butanol had been dissolved in 80 ml of anhydrous tetrahydrofuran was added at -60°C to 100 ml of liquid ammonia under an inert gas atmosphere and 1.79 g of lithium were added little by little. After reacting for 1 hour at a temperature of from -50 to -40°C, 35 ml of methanol were added and the ammonia was evaporated off, water was added to the residue and the mixture was extracted with ethyl acetate. The liquid extract obtained was washed with salt water and then dried using anhydrous sodium sulfate. The solvent was distilled off and then 30 ml of methanol, 45 ml of tetrahydrofuran and 10 ml of 3N hydrochloric acid were added and the mixture was stirred overnight. After reaction, water was added and the mixture was extracted with ethyl acetate and the extract was washed sequentially with

sodium bicarbonate solution and salt water and then dried using anhydrous sodium sulfate. The solvent was distilled off and then column chromatography (silica gel, 250 g) was carried out using ethyl acetate/hexane (25: 75 to 50 : 50) as the developing solvent and 3.81 g of the title compound were obtained as a white solid (yield 94%).

[0039]

Reference Example 6

The Synthesis of a Mixture of 17β-Ethyl-3-ethylidenedioxy-D-homo-oestra-5-ene-17a-one and 17β-Ethyl-3-ethylidenedioxy-D-homo-oestra-5(10)-ene-17a-one

A mixture of the 3.81 g of the 17β-ethyl-17aβ-hydroxy-D-homo-oestra-4-ene-3-one obtained in Reference Example 5, 3.74 g of ethylene glycol, 0.11 g of p-toluenesulfonic acid mono-hydrate and 250 ml of benzene was dehydrated by heating under reflux for 5 hours using Dean and Stark apparatus. After this reaction sodium bicarbonate solution was added and the organic layer was separated off and washed with saturated salt water and then dried with anhydrous sodium sulfate. The solvent was distilled off and then 50 ml of dimethylformamide and 7.16 ml of pyridinium dichromate were added and the mixture was stirred for 3 hours at room temperature. Water was added to the reaction mixture so obtained and it was then extracted with ethyl acetate, and after washing sequentially with aqueous sodium thiosulfate solution and salt water the extract was dried using anhydrous sodium sulfate. The solvent was distilled off and column chromatography (silica gel, 250 g) was carried out using ethyl acetate/hexane (20 : 80) as the developing solvent and 3.57 g of a mixture of the title compounds was obtained as a white solid (yield 82%).

[0040]

Reference Example 7

The Synthesis of 17β-Ethyl-17aα-ethynyl-17aβ-hydroxy-D-homo-oestra-4-ene-3-one

Anhydrous cerium chloride (7.40 g) was dried under reduced pressure for 1 hour at 140°C and then the system was displaced with argon. Next 50 ml of anhydrous tetrahydrofuran were added and the mixture was stirred overnight at room temperature. A tetrahydrofuran solution of lithium trimethylsilylacetylide which had been prepared from 2.95 g of trimethylsilylacetylene and 15.6 ml of n-butyllithium (1.6M hexane solution) was added dropwise to this white suspension at -70°C. After stirring for 1 hour at the same temperature, a solution obtained by dissolving the 3.57 g of the mixture of 17β-ethyl-3-ethylenedioxy-D-homo-oestra-5-ene-17a-one and 17β-ethyl-3-ethylenedioxy-D-homo-oestra-5(10)-ene-17a-one obtained in Reference Example 6 in 50 ml of anhydrous tetrahydrofuran was added dropwise. After stirring for 1 hour at the same temperature, 50 ml of water were added and the mixture was hydrolyzed. Water and ethyl acetate were added to the reaction mixture so obtained and the mixture was extracted with ethyl acetate. The organic layer was washed with salt water and then dried using anhydrous sodium sulfate. The residue obtained on distilling off the solvent was dissolved in 30 ml of tetrahydrofuran, 10 ml of tetrabutylammonium fluoride (1M tetrahydrofuran solution) were added and the mixture was stirred for 1 hour at room temperature. The reaction liquid so obtained was poured into water and extracted with ethyl acetate and then washed with salt water and dried using anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was dissolved in a liquid mixture of 20 ml of tetrahydrofuran and 30 ml of methanol, 15 ml of 3N hydrochloric acid were added and the mixture was stirred overnight at room temperature. After reaction, water was added and the mixture was extracted with ethyl acetate, washed sequentially with sodium bicarbonate solution and salt water and dried using anhydrous sodium sulfate. The solvent was

distilled off and then column chromatography (silica gel, 350 g) was carried out using ethyl acetate/hexane (25 : 75) as developing solvent and 2.92 g of the title compound which had the physical property values indicated below were obtained as a white solid (yield 86%).
Melting Point 265 - 267°C
^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.90 (3H, t, J = 8 Hz), 0.93 (3H, s), 2.50 (1H, s), 5.82 (1H, s)
[0041]
Example 4
The Synthesis of 3β-Acetoxy-17β-ethyl-17aα-ethynyl-D-homo-oestra-4-ene-17aβ-ol

A tetrahydrofuran solution (50 ml) of 1.47 g of the 17β-ethyl-17aα-ethynyl-17aβ-hydroxy-D-homo-oestra-4-ene-3-one obtained in Reference Example 7 was added dropwise, with ice cooling, to 30 ml of a tetrahydrofuran solution of 4.39 g of lithium tri-t-butoxyaluminium hydride and the mixture was stirred, with ice cooling, for 4 hours. Water was added to the reaction liquid so obtained and, after extraction with ethyl acetate, the organic layer was washed with saturated salt water and dried using anhydrous sodium sulfate. Then 0.68 g of pyridine, 0.66 g of acetic anhydride, 5 mg of 4-dimethylaminopyridine and 30 ml of methylene chloride were added to the residue obtained on distilling off the solvent and the mixture was stirred overnight at room temperature. The reaction liquid so obtained was washed sequentially with dilute hydrochloric acid, sodium bicarbonate solution and water and then dried using anhydrous sodium sulfate. The residue obtained in distilling off the solvent was subjected to silica gel column chromatography (hexane/ethyl acetate (4 : 1) as eluting solvent) and then recrystallized from methylene chloride/hexane and 0.93 g of the title compound which has the physical property values indicated above was obtained as colorless crystals (yield 56%).
Melting Point 202 - 204°C
^{1}H-NMR Spectrum (270 MHz, Heavy Chloroform, δ, ppm): 0.88 (3H, t, J = 8 Hz), 0.91 (3H, s), 2.07 (3H, s), 2.48 (1H, s), 5.15 - 5.25 (1H, m), 5.31 (1H, s)

[0042]
Example of Testing 1

The effect of the compounds of this invention was investigated using the bone formation promoting action of heterotopically induced bone for which bone morphogenic protein crudely refined from ox bone was used as an indicator.
(1) Crude Refinement of Bone Morphogenic Protein

The crude refinement of bone morphogenic protein was carried out using the method of Kuboki et al. ("Principles of Hard Tissue Rebuilding", pages 299 to 303 (published 1989), representative author Yoshinori Kuboki, publishing contact: Hokkaido University, Department of Dentistry, Oral Cavity Biochemistry Course.) That is to say, fresh ox leg bones were pulverized in liquid nitrogen and de-fatted with a liquid mixture of chloroform and methanol and then decalcified with hydrochloric acid and decalcified ox bone powder was obtained. Crude protein was extracted from the decalcified ox bone powder with 4M guanidine hydrochloride which contained A protease inhibiting agent. The crude protein so obtained was refined by means of hydroxyapatite column chromatography and a fraction which contained bone morphogenic protein was obtained. The bone morphogenic protein fraction was concentrated by means of the ultra-filtration method and dialysis was carried out against de-ionized water and the freeze dried

precipitate was used in the investigation outlined below as the crudely refined bone morphogenic protein.

(2) Investigation of Bone Formation Promoting Action Using Crudely Refined Bone Morphogenic Protein

Crudely refined bone morophogenic protein and rat decalcified bone guanidine hydrochloride extract reside were mixed together and sealed in a gelatin capsule. The capsule was implanted under the skin on the back of a castrated Wistar male rat. The compounds obtained in Example 1 and Example 4 were suspended as compounds for investigation in sesame seed oil and administered subcutaneously for 2 weeks from 3 weeks after the implantation. Just sesame seed oil was administered to a control group. The induced bone was excised the day after the administration had been completed and the bone salt content of the induced bone was estimated using bone salt determining apparatus (DSC-600, produced by the Aroka Co.) The results obtained are shown in Table 1, and in the cases where compounds of the present invention had been used the bone salt content of the induced bone was increased when compared with the control group, and it was clear that the compounds of the invention had a bone mass increasing effect.

[0043]

Table 1

Compound Under Investigation	Dose Rate (mg/kg/day)	Bone Salt Content of Induced Bone with Respect to the Control Group (%)
Compound of Example 1	10	134
	20	148
Compound of Example 4	10	118
	20	129

[0044]

Example of Preparation Formulation 1

Tablets

Compound of Example 1	10 g
Lactose	20 g
Starch	98 g
Carboxymethylcellulose calcium	20 g
Magnesium stearate	2 g

The abovementioned components were mixed together in the usual way and tablet stamping was carried out to produce 1,000 tablets which contained 10 mg of the compound of Example 1 per tablet.

[0045]

Example of Preparation Formulation 2

Capsules

Compound of Example 2	10 g
Lactose	80 g
Starch	95 g
Hydroxypropylcellulose	10 g
Magnesium stearate	5 g

The abovementioned components were mixed together in the usual way and formed into granules and these were packed into No. 3 capsules at a rate of 200 mg per

capsule to produce 1000 capsules which contained 10 mg of the compound of Example 2 per capsule.

[0046]

Preparation Formulations Examples 3 and 4

Capsules

Capsules were produced in the same way as before but with the compound of Example 2 in Preparation Formulation Example 2 being replaced with the compound of Example 3 (Preparation Formulation Example 3) or the compound of Example 4 (Preparation Formulation Example 4).

[0047]

Effect of the Invention

The steroid derivatives of this invention exhibit an excellent bone mass increasing action and, since they have little in the way of side effects, they are useful as safe drugs for the treatment of osteoporosis.